Clinical Medicine Insights: Case Reports

CASE REPORT

Leiomyomatosis Peritonealis Disseminata Associated with Endometriosis and Multiple Uterus-Like Mass: Report of Two Cases

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Abstract: Leiomyomatosis peritonealis disseminate (LPD) is a rare benign disease of unknown etiology of women in reproductive age. A few reported cases of association with endometriosis have been described suggesting a possible origin from submesothelial multipotential cells. We present two cases of LPD associated with endometriosis expressing smooth muscle metaplasia, and some of the nodules with aspects of uterus-like mass. Laparoscopy, gross findings, and the pathological and immunohistochemical study of the surgical specimens were described. Our findings suggest an endometriotic origin for the LPD and indicate that the therapeutic approach might contemplate the surgical reduction of the nodules and endometriosis treatment.

Keywords: leiomyomatosis peritonealis disseminata; endometriosis; uterus-like mass; immunohistochemistry; laparoscopy; smooth muscle metaplasia

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Introduction

Leiomyomatosis peritonealis disseminata (LPD) is a rare benign disease of unknown etiology in women of reproductive age.[1] It is characterized by multiple subperitoneal or peritoneal smooth muscle tumors of varying sizes on the omentum and peritoneal surfaces. A possible origin from submesothelial multipotential cells has been suggested, although it is not clear if the stimulus to smooth cell differentiation is hormonal, genetic, or both.[1,2] The few reported cases of association between LPD and endometriosis favor a hypothesis of a common origin for both the lesions.[2–6] However, the mechanisms involved in this association are unknown. It is not clear whether the leiomyomatous nodules originate from the endometriosis foci, or if both the conditions correspond to different clinicopathological presentations of a common metaplastic phenomenon. Another extremely rare condition, also possibly originating from the submesothelial multipotential cells, is the uterus-like mass, defined as an extrauterine mass composed of smooth muscle and a central cavity lined by endometrium, resembling a normal uterus.[7–10] The peritoneal localization of benign smooth muscle cells lesions, such as leiomyomas or uterus-like mass, is an intriguing fact that offers an unique opportunity to understand the mechanisms of extrauterine mullerian differentiation, known as mullerianosis.[9] In this study, we describe two cases of LPD associated with endometriosis, with some of the nodules resembling uterus-like mass, and with clear evidence of smooth-muscle metaplasia in the stromal component of endometriosis. Furthermore, we discuss the origin of peritoneal smooth muscle lesions from endometrial stroma.

Methods and Case Reports

We describe two cases referred to one of the authors (FMC) to review the hematoxylin-eosin slides and perform the immunohistochemical study.

Case 1—A 32-year-old previously healthy nulliparous woman, who had a history of abnormal vaginal bleeding in 2004. In that occasion, she was submitted to a hysteroscopic myomectomy. She remained asymptomatic until 2008, when she presented a pelvic mass of 86.0 mm at ultrasound examination, associated with serum CA-125 of 138 U/mL. At laparoscopy, there were innumerable nodules involving pelvic and abdominal peritoneal surfaces, omentum, and the left ovary, varying from few millimeters up to 50.0 mm. Some of the nodules were associated with the central cystic cavities filled with dark brown viscous fluid. There were also classical peritoneal endometriotic lesions of red flame-like type. Some of the nodules had been excised for pathological study. After the diagnosis, she received goserelin for 6 months. The control magnetic resonance imaging (MRI) showed significant reduction in the nodules and the CA-125 was normal. Fifteen months later, the serum CA-125 was 36.0 U/mL and the MRI revealed a left ovarian mass of 65.0 mm associated with multiple pelvic nodules measuring up to 45.0 mm in diameter. Computed tomography (CT) scan of the lungs showed 28 nodules (Fig. 1). She received goserelin for another 6 months, but CT scan did not show any change in the lesions. Now, she has been taking anastrozole for 6 months, with stable disease. The last serum CA-125 was 69.1 U/mL.

Case 2—A 41-year-old woman was submitted to laparoscopy for surgical treatment of deep infiltrating endometriosis involving rectovaginal space, ovary, peritoneum and rectosigmoid. She complained of pelvic pain, dysmenorrhea, intestinal transit disturbances and proctalgy. There was no sign or symptom of anemia, weight loss, or weakness. At laparoscopy, there were innumerable nodules ranging from few millimeters to 20.0 mm, involving all the peritoneal surfaces, although more numerous in the pelvis, and not infiltrative in the subjacent viscera. Greater and lesser omentums were extensively involved. The nodules were solid, firm, and white,

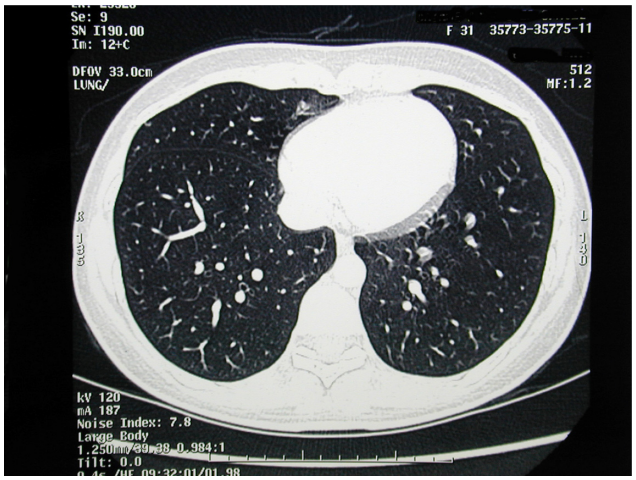

Figure 1. CT scan of lungs showing numerous nodules.

but some of those localized in the left paracolic gutter were darker, suggesting being filled with hemorrhagic material (Fig. 2). There were peritoneal superficial endometriotic lesions and an endometriotic ovarian cyst at the left side measuring 25.0 mm. As the lesions were unresectable, we carried out left salpingooophorectomy and partial excision of the lesions in the left paracolic gutter, vesicouterine peritoneum, and pouch of Douglas. The specimen was sent for pathological examination. Patient has been receiving medroxyprogesterone for 4 months without signs of disease progression.

Pathological Study

Microscopic examination of the lesions of the two cases was very similar and characterized by multiple nodular proliferation comprising bundles of spindle-shaped smooth muscle cells, without atypia, necrosis, or mitosis. The nodules were embedded in fat tissue, and were mostly well circumscribed, but some of them had an infiltrative border (Fig. 3A and B). Some nodules presented central area with stromal and epithelial endometrial tissue admixed with the smooth muscle cells, creating an aspect of the uterine corpus wall (Fig. 3C and D). Some glands were cystically dilated. Variable amounts of blood, necrotic-appearing endometrium, fibrosis, and hemosiderin-laden macrophages were associated with the endometrial tissue.

We selected to immunohistochemistry study either areas of pure leiomyoma as sections of the lesions containing both the components (smooth muscle and endometrial). The histological sections were immunostained for estrogen receptor (ER), progesterone receptor (PR), CD10 (Common Acute Lymphocytic Leukemia Antigen or CALLA), smooth muscle actin (SMA), desmin, CD117 (c-kit), calretinin, Wilms' tumor suppressor gene (WT1), Protein gene product (PGP 9.5), and Ki-67. The sources and dilutions of the antibodies and epitope retrieval methods used are listed in Table 1. Bound antibodies for ER, PR, Ki-67, WT1, CD17, CD10, and PGP 9.5 were detected using Novolink method (Leica, USA). For calretinin, we used Envision (Dako, USA) and for SMA and desmin we used avidin-biotin complex (ABC) method (Vector, USA). Negative and positive controls were used for each antibody. For positive controls we use archival human tissues proved positive for the desired antigen. For negative controls, the primary antibody was omitted.

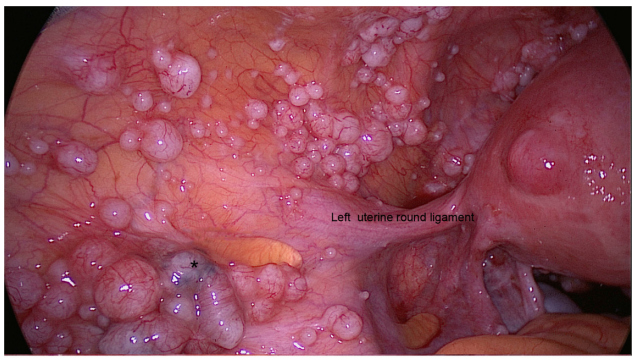

Figure 2. Laparoscopic image of Case 2 showing multiple nodules of various sizes on the peritoneal surfaces, characteristic of leiomyomatosis peritoneal disseminata, one of them (*) associated with endometriosis.

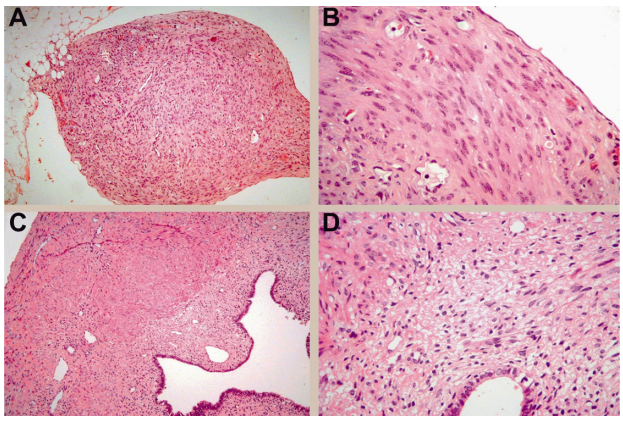

Figure 3. Microscopic presentation of the nodules. (**A**) Well-circumscribed leiomyomatous nodule attached to peritoneal surface, focally infiltrative in the subjacent adipose tissue (original magnification 100×). (**B**) Magnification of the nodule in A (original magnification 400×). (**C**) Nodule composed of smooth muscle tissue in the periphery associated with the central area of stromal and glandular endometrial tissue, mimicking corpus uterine wall (original magnification 100×). (**D**) Magnification of nodule in C showing the transition between stromal endometrial and smooth muscle component (original magnification 400×).

On immunohistochemistry examination, spindle cells of smooth muscle areas were strongly positive for desmin (Fig. 4A), smooth muscle actin (SMA), WT-1, ER and PR. Few smooth muscle cells were also positive for CD10 and CD117. The endometrial stromal cells were diffusely positive for CD10 (Fig. 4B), ER, PR, smooth muscle actin (Fig. 4C), and WT-1. The stromal endometrial component showed scattered morphological endometrial spindle cells with immunoexpression of desmin (Fig. 4D). Both the mesenchymal components were negative for calretinin and PGP 9.5. The glands were diffusely positive for ER and PR.

Table 1. Reagents and methods used for immunohistochemical analysis.

Antigen	Clone/source	Dilution	Epitope retrieval method
ER (estrogen receptor)	SP1/Neomarkers	1:1000	Pressure cooker
PR (progesterone receptor)	PgR636/Dako	1:1600	Pressure cooker
CD10	270/Novocastra	1:200	Steamer 60
Smooth muscle actin	1A4/Dako	1:600	Steamer 60
Desmin	D33/Dako	1:3200	Microwave oven
c-kit (CD117)	Polyclonal/Dako	1:450	Microwave oven
Calretinin	SP13/Neomarkers	1:400	Steamer 60
WT-1	6FH2/Dako	1:400	Pressure cooker
Protein gene product (PGP 9.5)	Polyclonal/Dako	1:3200	Steamer 60
Ki-67	MIB1/Dako	1:4800	Pressure cooker

Pressure cooker: Citrate buffer (pH 6) (*Tender Cooker, Nordic Wave*, USA); Microwave: Citrate buffer (pH 6), 15 min (Eletrolux, 900W).

Discussion

Multiple peritoneal leiomyomas were first described in a case report in 1952, as a feature associated with a granulosa cell ovarian tumor.[11] However, only in 1965, the condition was named "leiomyomatosis peritonealis disseminata" and characterized as an entity related to uterine leiomyomas.[12] Since then, isolated cases have been described, without consensus about the histogenesis of this rare condition. First, it was suggested that LPD corresponded to a benign reparative process in which fibroblasts replaced subperitoneal deciduas.[13] The first case of LPD associated with endometriosis was described in 1980, when the authors suggested a metaplasia of the subcoelomic mesenchyme in the pathogenesis of the peritoneal smooth cell lesions.[14] The largest series of LPD was published in 1982.[15] The authors described 20 patients with an age ranged from 22 to 41 years; half of them were pregnant or immediately postpartum. Most of the nodules were composed of smooth muscle cells, but myofibroblasts, fibroblasts, collagen and decidual stromal cells were also noted. One of the patients had extensive endometriosis, including stromal endometrial cells associated with smooth muscle nodules. However, the authors interpreted this association as very rare and probably unrelated. On the other hand, they discussed the role of primitive mesenchymal stem cell as the origin of fibroblasts, myofibroblasts, stromal endometrial cells, decidual cells, and even endometrial glandular epithelium. In that study, the authors emphasized the hormonal role in the initiation and/or promotion of the LPD.[15] Various reports of association between LPD and endometriosis have been described, reinforcing the theory of metaplastic origin of LPD.[2–6,14] However, it is difficult to admit that a rare disease, such as LPD, can have the same origin and hormonal influence as that of endometriosis, an extremely common condition. On the other hand, smooth muscle metaplasia is an event recognizable in stromal endometriosis,[16] which could be demonstrated in our cases. We can postulate that LPD is a rare event in the spectrum of endometriosis, and we can speculate that even those cases where endometrial tissue is not found can correspond to a special clinicopathological form of this disease. However, we cannot ignore the important insights of Batt et al[17] when defining the mullerianosis condition—misplaced endometrial or mullerian tissue—and the possible explanation for the

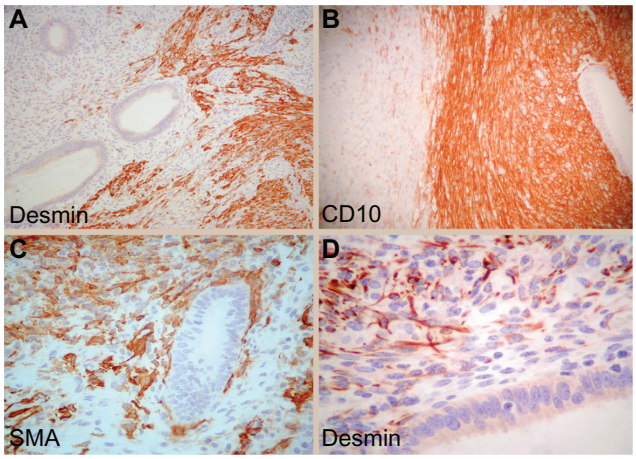

Figure 4. Immunohistochemical study. (**A**) Smooth muscle cells strongly positive to desmin (original magnification 100×). (**B**) Endometrial stroma inside the leiomyomatous nodule positive to CD10 (original magnification 100×). (**C**) Endometrial stroma cells positive to Smooth Muscle Actin (SMA) (original magnification 100×). (**D**) Scattered endometrial stromal cells of the endometriotic tissue positive to desmin (original magnification 400×).

extrauterine uterus-like mass, according this concept, as a development entity.[9] Our endometriosis foci within the smooth muscle nodules showed evidence of muscle metaplasia, and besides, the transition between both the components were not well demarcated and the borders of the muscle nodules were infiltrative at times, a finding more likely to be observed in endometriosis than in a development entity, such as mullerianosis. Clement, in his excellent review about endometriosis, recognizes smooth muscle metaplasia, that can be focal or extensive, constituting entities like endomyometriosis and uterus-like mass.[18] The extensive replacement of the stromal component of endometriosis was initially described by Cozzutto in 1981.[19] In the same year, Rohlfing described the same association with the description of nodules resembling uterus miniature.[20] The uterus-like mass is characterized by a central cavity lined by endometrium surrounded by a thick wall composed of smooth muscle and is still a very rare condition with a questionable histogenesis.[8–10,16,21,22] Our cases show the classical presentation of LPD, but some of the nodules share many similarities with miniature uterus. The association with endometriosis are more striking than some of the previously reports[2,3,5,15] and the aspects of classical endometriosis and LPD merge subtlety with the uterus-like appearance. The clinical evolutions of the two cases as the gross presentation of the disease are highly consistent with endometriosis. Besides, the pathological findings clearly demonstrate the endometriosis associated with smooth muscle metaplasia and transition between stromal endometriotic cells and muscle nodules. It is possible that most of the LPD cases, even those without a clear association with endometriosis, correspond to a variant of the endometriosis disease. Other explanations have been suggested, such as a possible iatrogenic cause for the disease.[1] This latter hypothesis invites us to think about a possible parallel between the implant theory of endometriosis and the smooth muscle implants occurring in leiomyoma morcellation, as suggested by Al-Talib and Tulandi.[1] A possible implantation theory is consistent with the role of mullerian stem cells located in topic endometrium as the generator of most of the cases of endometriosis and, probably, also the LPD as well. This possible relation to endometriosis might be considered at the moment of therapeutic planning. Although there is no consensus about the ideal management of LPD,[1] surgery and estrogenic suppression are the mainstay. Hormonal treatment includes GnRH, aromatase inhibitors, and megestrol acetate, and has been described as useful in many cases.[23–26] Similar to endometriosis, some cases of LPD can be resistant to hormonal suppression, and some lesions can present local and distant recurrences.[27] For such aggressive cases, chemotherapy with doxorubicin and carbazine can be administered.[27]

Conclusions

Our findings suggest an endometriotic origin for the LPD and indicate that the therapeutic approach might contemplate surgical reduction of the nodules and endometriosis control. Treatment could be started by decreasing the estrogen level either by the administration of GnRHa or an aromatase inhibitor. In severe cases, particularly those not responsive to hormonal blockage, oophorectomy must be considered.

Author Contributions

Conceptualization of the study: FMC, JPC. Surgeon of Case 2: RMAP, BC. Consultant of Case 1: RL, ECB. Pathological and immunohistochemistry study: FMC. Joint development of the structure and arguments of the paper: FMC, JPC. Preparation of the first draft of the manuscript: FMC. Contribution to the writing of the manuscript: JPC, ECB. Critical revisions and approval of the final version: RMAP, ECB, BC, RL. All authors reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References

1. Al-Talib A, Tulandi T. Pathophysiology and possible iatrogenic cause of leiomyomatosis peritonealis disseminata. *Gynecol Obstet Invest*. 2010;69: 239–44.
2. Haberal A, Kayikcioglu F, Caglar GS, Cavusoglu D. Leiomyomatosis peritonealis disseminata presenting with intravascular extension and coexisting with endometriosis: a case report. *J Reprod Med*. 2007;52:422–4.
3. Dauge MC, Delmas V, Grossin M, Rubinstajn B, Moulonguet A, Bocquet L. Disseminated peritoneal leiomyomatosis associated with endometriosis. Apropos of a case. *Ann Pathol*. 1986;6:221–4.
4. Gana BM, Byrne J, McCullough J, Weaver JP. Leiomyomatosis peritonealis disseminata (LPD) with associated endometriosis: a case report. *J R Coll Surg Edinb*. 1994;39:258–60.
5. Herrero J, Kamali P, Kirschbaum M. Leiomyomatosis peritonealis disseminata associated with endometriosis: a case report and literature review. *Eur J Obstet Gynecol Reprod Biol*. 1998;76:189–91.
6. Zotalis G, Nayar R, Hicks DG. Leiomyomatosis peritonealis disseminata, endometriosis, and multicystic mesothelioma: an unusual association. *Int J Gynecol Pathol*. 1998;17:178–82.
7. Liang YJ, Hao Q, Wu YZ, Wu B. Uterus-like mass in the left broad ligament misdiagnosed as a malformation of the uterus: a case report of a rare condition and review of the literature. *Fertil Steril*. 2010;93:1347. e13–6.
8. Kaufman Y, Lam A. The pelvic uterus-like mass—a primary or secondary Müllerian system anomaly? *J Minim Invasive Gynecol*. 2008;15:494–7.
9. Batt RE. Pathogenesis of a parauterine uterus-like mass: developmentally misplaced müllerian tissue—müllerianosis. *Fertil Steril*. 2010;94:e45.
10. Ahmed AA, Swan RW, Owen A, Kraus FT, Patrick F. Uterus-like mass arising in the broad ligament: a metaplasia or mullerian duct anomaly? *Int J Gynecol Pathol*. 1997;16:279–81.
11. Willson Jr, Peale Ar. Multiple peritoneal leiomyomas associated with a granulosa-cell tumor of the ovary. *Am J Obstet Gynecol*. 1952;64:204–8.
12. Taubert Hd, Wissner Se, Haskins Al. Leiomyomatosis Peritonealis Disseminata; An Unusual Complication Of Genital Leiomyomata. *Obstet Gynecol*. 1965;25:561–74.
13. Parmley TH, Woodruff JD, Winn K, Johnson JW, Douglas PH. Histogenesis of leiomyomatosis peritonealis disseminata (disseminated fibrosing deciduosis). *Obstet Gynecol*. 1975;46:511–6.
14. Kuo T, London SN, Dinh TV. Endometriosis occurring in leiomyomatosis peritonealis disseminata: ultrastructural study and histogenetic consideration. *Am J Surg Pathol*. 1980;4:197–204.
15. Tavassoli FA, Norris HJ. Peritoneal leiomyomatosis (leiomyomatosis peritonealis disseminata): a clinicopathologic study of 20 cases with ultrastructural observations. *Int J Gynecol Pathol*. 1982;1:59–74.
16. Fukunaga M. Smooth muscle metaplasia in ovarian endometriosis. *Histopathology*. 2000;36:348–52.
17. Batt RE, Smith RA, Buck Louis GM, Martin DC, Chapron C, Koninckx PR, et al. Müllerianosis. *Histol Histopathol*. 2007;22:1161–6.
18. Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. *Adv Anat Pathol*. 2007;14:241–60.
19. Cozzutto C. Uterus-like mass replacing ovary: report of a new entity. *Arch Pathol Lab Med*. 1981;105:508–11.
20. Rohlfing MB, Kao KJ, Woodard BH. Endomyometriosis: possible association with leiomyomatosis disseminata and endometriosis. *Arch Pathol Lab Med*. 1981;105:556–7.
21. Redman R, Wilkinson EJ, Massoll NA. Uterine-like mass with features of an extrauterine adenomyoma presenting 22 years after total abdominal hysterectomy-bilateral salpingo-oophorectomy: a case report and review of the literature. *Arch Pathol Lab Med*. 2005;129:1041–3.
22. Takeda A, Imoto S, Mori M, Yamada J, Nakamura H. Uterus-like mass of ovarian ligament: Image diagnosis and management by laparoendoscopic single-site surgery. *J Obstet Gynaecol Res*. 2011;37:1895–9.
23. Hales HA, Peterson CM, Jones KP, Quinn JD. Leiomyomatosis peritonealis disseminata treated with a gonadotropin-releasing hormone agonist. A case report. *Am J Obstet Gynecol*. 1992;167:515–6.
24. Clavero PA, Nogales FF, Ruiz-Avila I, Linares J, Concha A. Regression of peritoneal leiomyomatosis after treatment with gonadotropin releasing hormone analogue. *Int J Gynecol Cancer*. 1992;2:52–4.
25. Parente JT, Levy J, Chinea F, Espinosa B, Brescia MJ. Adjuvant surgical and hormonal treatment of leiomyomatosis peritonealis disseminata. A case report. *J Reprod Med*. 1995;40:468–70.
26. Takeda T, Masuhara K, Kamiura S. Successful management of a leiomyomatosis peritonealis disseminata with an aromatase inhibitor. *Obstet Gynecol*. 2008;112:491–3.
27. Lin YC, Wei LH, Shun CT, Cheng AL, Hsu CH. Disseminated peritoneal leiomyomatosis responds to systemic chemotherapy. *Oncology*. 2009;76: 55–8.